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EXAMINER	
KERR, KATHLEEN M	
ART UNIT	**PAPER NUMBER**
1652	

DATE MAILED: 10/21/2003

15

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/942,407	SANTI ET AL.	
	Examiner	Art Unit	
	Kathleen M Kerr	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 July 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *26-45* is/are pending in the application.

4a) Of the above claim(s) *26-42* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *43-45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *8* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *BLAST alignment* .

DETAILED ACTION

Application Status

1. In response to the previous Office action, a written restriction requirement (Paper No. 9, mailed on June 6, 2003), Applicants filed an election received on July 21, 2003 (Paper No. 12). Claims 26-45 are pending in the instant Office action.

Election

2. Applicant's election without traverse of Group II, Claims 43-45, in Paper No. 12 is acknowledged.

Claims 26-45 are pending in the instant application. Claims 26-42 are withdrawn from further consideration as non-elected inventions. Claims 43-45 will be examined herein.

Priority

3. The instant application is granted the benefit of priority for U.S. non-provisional application 09/699,136 filed on October 27, 2000 and for U.S. provisional application 60/161,703 filed on October 27, 1999 as requested in the declaration and the first lines of the specification. However, priority to U.S. Provisional Application Nos. 60/161,414 and 60/206,082 filed on October 25, 1999 and May 18, 2000, respectively, is **NOT** granted because said application was filed more than 1 year before the filing of the instant application and/or no inventors are in common.

The Examiner notes that the first paragraph of the specification correctly relates priority data and "related case" data.

Information Disclosure Statement

4. The information disclosure statement filed on August 29, 2001 (Paper No. 8) has been reviewed, and its references have been considered as shown by the Examiner's initials next to each citation on the attached copy.

Compliance with the Sequence Rules

5. By virtue of the amendment filed on August 29, 2003, this application fully complies with the sequence rules.

Objections to the Specification

6. The specification is objected to because the title is not descriptive. A new title is required that is clearly indicative of the invention to which the elected claims are drawn (see M.P.E.P. § 606.01). The Examiner suggests the following new title:

---Methods for Converting (R)-Methylmalonyl CoA to (S)-Methylmalonyl CoA using a Methylmalonyl CoA Epimerase Gene---

7. In the specification, the Abstract is objected to for not completely describing the disclosed subject matter. It is noted that in many databases and in foreign countries, the Abstract is crucial in defining the disclosed subject matter, thus, its completeness is essential. The Examiner suggests the inclusion of the gene names, such as methylmalonyl CoA epimerase from *Propionibacterium shermanii*, birA (biotin transferase) and methylmalonyl CoA mutase, and the inclusion of particular kinds of cells used for completeness.

8. The specification is objected to for containing figures/graphs embedded within the text.

a) On page 58, a figure is disclosed.
b) On page 59, a graph is disclosed.
c) On page 62, a graph is disclosed. Also, the description of this graph of page 62 includes colors that are not reflected in the graph itself.
d) On page 74, a figure is disclosed.
e) On page 82, a graph is disclosed.
f) On page 83, a graph is disclosed.
g) On page 84, a figure is disclosed.
h) On page 87, a figure is disclosed.

Appropriate correction to the specification is required.

9. The specification is objected to for the following inconsistencies:

a) On page 76, a schematic "above" is referred to, but it unclear to which figure the schematic refers.
b) On page 75-86 and 88, numbered references are noted ([3]) with references being found on pages 90-92; however, throughout the rest of the specification, citations are noted throughout the text and not by number (endnote). Consistency is reference citation is required.
c) On page 9, reference 15 is incomplete.

Correction is required.

10. The specification is objected to for inappropriate notation of an internet address. On page 48, lines 17-18, an internet address is cited in an unacceptable form. See M.P.E.P. § 707.05(e) for the acceptable notation of an internet address.

Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claims 43-45 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 43 depends from a cancelled claim, Claim 22, The claim will be examined as if Claim 43 depends from the broadest, pending host cell claim, that is Claim 30.

It is noted that Claim 30, as well as Claims 29 and 26, are non-elected subject matter. All their limitations have been interpreted into Claim 43 for examination purposed and must be amended into Claim 43 in response to this Office action.

12. Claims 43-45 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The instant claims are confusing as to how they make the S isomer in view of the instant specification. On page 70, lines 10-28, an assay is described in which a mixture of R/S is fed to appropriate host cells and the S isomer is consumed at the expense of NADH. Thus, by this description, it would seem that S is converted into R, not R to S as required by the claims. Clarification is required.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

13. Claim 43 is rejected under 35 U.S.C. § 112, first paragraph, written description, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The instant claim is drawn to methods using a host cells transformed with genes that are claimed solely by function and without any structural limitations using the enzyme name and methylmalonyl CoA epimerase from *Propionibacterium shermanii*. Clearly, the scope of Claim 43 intends to include more than methods using the DNA species disclosed in the specification, that of DNA encoding SEQ ID NO:2, based on the further limiting claim, Claim 45.

The Court of Appeals for the Federal Circuit has recently held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as be structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." University of California v. Eli Lilly and Co., 1997 U.S. App. LEXIS 18221, at *23, quoting Fiers v. Revel, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original). To fully describe a genus of genetic material, which is a chemical compound, applicants must (1) fully describe at least one species of the claimed genus sufficient to represent said genus whereby a skilled artisan, in view of the prior art, could predict the structure of other species encompassed by the claimed genus and (2) identify the common characteristics of the claimed molecules, e.g., structure, physical and/or chemical

characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these.

In the instant specification, a gene encoding methylmalonyl CoA epimerase from P. shermanii is fully described as SEQ ID NO:1 and/or any DNA encoding SEQ ID NO:2. The specification also describes other epimerases, from *S. coelicolor* and *B. subtilis*, but these are not within the metes and bounds of the claimed invention. Thus, a single species (or variable species within the degeneracy of the genetic code) of the claimed method is described. The epimerase genes are only described according to the functional characteristics of the enzymes they encode; no structural relationship is described or used in the claims. Thus, one of skill in the art would be unable to predict the structure of other members of this genus, specific to *P. shermanii*, by virtue of the instant disclosure. Therefore, claims drawn to methods using host cells containing this genus of genes are also not adequately described.

14. Claim 43 is rejected under 35 U.S.C. § 112, first paragraph, scope of enablement, because the specification, while being enabling for methods using a gene encoding SEQ ID NO:2, does not reasonably provide enablement for methods using a *P. shermanii* gene encoding a methylmalonyl CoA epimerase. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims. To practice the methods to the full extent of their scope, one is required to make genes (other than those encoding SEQ ID NO:2) from *P. shermanii* encoding a methylmalonyl CoA epimerase. To do so would require undue experimentation.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The Court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

The instant specification teaches SEQ ID NO:2, methylmalonyl CoA epimerase from *P. shermanii*, and SEQ ID NO:1, a *P. shermanii* gene exactly encoding SEQ ID NO:2. The art includes few examples of methylmalonyl CoA epimerase encoding genes. The art fully enables any DNA encoding SEQ ID NO:2 based on the degeneracy of the genetic code. While the instant specification describes and enables means for identifying other methylmalonyl CoA epimerase genes using hybridization methods, etc., these methods do not enable one of skill in the art to make all, or a relevant portion of, the polynucleotides within the scope of the claims

because the ability to find a methylmalonyl CoA epimerase gene, which is structurally related to SEQ ID NO:1, is not equivalent to the ability to make a methylmalonyl CoA epimerase gene as required by the statute (i.e., "make and use"). No description in the specification or the art provides particular residues whose encoding is important within the disclosed sequence so that its methylmalonyl CoA epimerase-nature is maintained. Thus, one of skill in the art would be unable to predict the structure of the other members of the genus in order to make such members. Therefore, the instant claims are not enabled to the full extent of their scope.

Claim Rejections - 35 U.S.C. § 103

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

15. Claim 43 is rejected under 35 U.S.C. §. 103(a) as being unpatentable over Leadlay (1981-see IDS) in view of the combined teachings of Matsudaira ("Limited N-Terminal Sequence Analysis." Methods in Enzymology (1990) 182:602-613), Wozney ("Using Purified Protein to Clone Its Gene." Methods in Enzymology (1990) 182:738-751), and Maniatis *et al.* (in Molecular Cloning: A Laboratory Manual (1982) pages 404-435). The instant claims are drawn to methods of making (S)-methylmalonyl CoA in a host cell that expresses a *P. shermanii* methylmalonyl CoA epimerase. Since all host cells naturally contain (R)-methylmalonyl CoA, expression of an active epimerase protein inherently practices the method step of converting.

Leadlay teaches the purification of a methylmalonyl-CoA epimerase from *Propionibacterium shermanii* to homogeneity (see Abstract).

The skill of an artisan in the field of molecular biology at the time the invention was made was such that the artisan could use conventional techniques to: 1) obtain a partial amino acid sequence of a polypeptide; 2) synthesize a degenerate polynucleotide probe based on the partial amino acid sequence; 3) use the polynucleotide probe to screen a cDNA or genomic library and identify a full length cDNA or genomic clone; 4) construct expression vectors comprising the isolated cDNA or genomic clone; and 5) transform a host cell with an expression vector comprising the isolated cDNA or genomic clone. Specifically, Matsudaira teaches methods for the determination of N-terminal amino acid sequences (see pages 602-604), and Wozney teaches methods of using purified proteins to clone the corresponding genes (see page 738). Wozney teaches the considerations for the selection of peptide candidates for the production of degenerate oligonucleotide probes, synthesis of oligonucleotide probes, screening of genomic or cDNA libraries, and isolation and amplification of cDNA or genomic clones. (see pages 738-751). The teachings of the Matsudaira and Wozney teach methods that enable the skilled artisan at the time the invention was made to produce the DNA fragments that encode the methylmalonyl-CoA epimerase protein as taught by Leadlay. Thus, the teachings of purified methylmalonyl-CoA epimerase by Leadlay render any, generic DNA fragments encoding said methylmalonyl-CoA epimerase protein obvious, because the prior art teachings suggest all the elements of said DNA fragments, and the prior art teachings enabled the artisan to produce said DNA fragments.

Maniatis *et al.* teach vectors, promoters and DNA sequences required for the transcription of cloned copies of genes, generally, and the translation of their mRNAs in *Escherichia coli* (see pages 404-411) and eukaryotic cells (see pages 412-433). Maniatis *et al.* also teach methods of maximizing the expression of cloned genes in transformed host cells (see page 431). The teachings of the Maniatis *et al.*, in light of the above teachings of Matsudaira and Wozney, teach methods that enable the skilled artisan at the time the invention was made to produce *P. shermanii* methylmalonyl-CoA epimerase-encoding DNA fragments in plasmids for recombinant expression of *P. shermanii* methylmalonyl-CoA epimerase which protein is taught by Leadlay. Thus, the teaching of a of *P. shermanii* methylmalonyl-CoA epimerase by Leadlay renders the DNA fragments encoding *P. shermanii* methylmalonyl-CoA epimerase and their use in the recombinant expression of *P. shermanii* methylmalonyl-CoA epimerase in host cells obvious, because the prior art teachings suggest all the elements of the DNA fragments and their use, and the prior art teachings enabled the artisan to produce the DNA fragments and recombinantly express them in host cells.

It would have been obvious to combine the above teachings to produce the claimed invention because of the common techniques used in the art. One of ordinary skill in the art at the time the invention was made would have been motivated to combine the teachings of Leadlay and with supporting references Matsudaira, Wozney, and Maniatis *et al.*, to formulate a better, recombinant method for producing a *P. shermanii* methylmalonyl-CoA epimerase because plasmid expression of *P. shermanii* methylmalonyl-CoA epimerase in a recombinant host cell is a more stable, continuous, and efficient mechanism for producing *P. shermanii* methylmalonyl-CoA epimerase. One would have had a reasonable expectation of success using

the disclosure of Leadlay and the instant references as born out by the instant disclosure and the procedures taught in the cloning of the epimerase gene.

The Examiner notes that any claim having, as a specific limitation, (1) exact DNA sequence or (2) a DNA encoding an exact amino acid sequence (see Claims 44-45) is **not** rendered obvious using the above analysis in view of *In re* Deuel (34 USPQ2d 1210) wherein claims having limitations drawn to sequence, either amino acid or DNA, cannot be made obvious by a general disclosure, absent sequence, of the protein or DNA.

Other References Cited

16. The following references are cited to complete the record:

a) Dayem *et al.* Metabolic Engineering of a Methylmalonyl-CoA Mutase-Epimerase Pathway for Complex Polyketide Biosynthesis in *E. coli.* Biochemistry (2002) 41:5193-5201.
b) GenBank Accession Number AY046899. *Propionibacterium freudenreichii subsp. shermanii* methylmalonyl CoA epimerase gene, complete cds (July 30, 2002).
c) Davis. The structural genes for methylmalonyl-CoA metabolism in Propionibacterium shermanii. (1986) Ph.D. Dissertation, University of Cambridge.
d) GenBank Accession Number AF454511. *Propionibacterium freudenreichii subsp. shermanii* methylmalonyl CoA epimerase gene, complete cds (January 3, 2002). See also attached BLAST alignment showing AF454511 is identical to AY046899 (above).
e) Allen *et al.* The isolation, purification, and properties of methylmalonyl racemase. J. Biol. Chem. (1963) 238:1637-1642.
f) Allen *et al.* Methylmalonyl-CoA Racemase from *Propionibacterium shermanii.* Methods in Enzymology (1969) 13:194-198.
g) McCarthy *et al.* Crystal Structure of Methylmalonyl-Coenzyme A Epimerase from *P. shermanii.* Structure (2001) 9:637-646.

Conclusion

17. Claims 43-45 are not allowed for the reasons identified in the numbered sections of this Office action. Applicants must respond to the objections/rejections in each of the numbered sections in this Office action to be fully responsive in prosecution.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kathleen M Kerr whose telephone number is (703) 305-1229. The examiner can normally be reached on Monday through Friday, from 8:30am to 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathupura Achutamurthy can be reached on (703) 308-3804. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-0294 for regular communications and (703) 305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

KMK
October 17, 2003